Of mice and human embryos

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human reproduction **OPINION**

Of mice and human embryos: is there an ethically preferred order of preclinical research on new assisted reproductive technologies?

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ABSTRACT: It is widely acknowledged that the responsible introduction of new assisted reproductive technologies (ARTs) requires preclinical safety research, including the use of animal models and human embryos. However, the moral sensitivity of human embryo research has led to regulations and guidance stating that human embryos may only be used for research that cannot also be conducted with animals. We call this the 'use animals first' (UAF) rule. In the field of ART research, this translates into the notion of an ideal chain of consecutive preclinical research steps, where research using human embryos may only be considered as a further step after promising results have been obtained in animals first. This may lead to research ethics committees requiring animal studies that are in fact a waste of time and money, while exposing animals to an infringement of their wellbeing for no good purpose. In this paper, we explore the possible moral arguments behind the UAF-rule and test their validity. We conclude that there are no convincing grounds for upholding this rule and recommend replacing it.

Key words: ethics / assisted reproductive technologies / preclinical research / animal research / human embryo research / responsible innovation

Introduction

An important concern with developments in medically assisted reproduction is that new techniques or add-ons to existing ones are often introduced without sufficient preclinical safety and efficacy studies, and also without meaningful efforts to collect follow-up data. As several authors have pointed out, the field fails to meet standards of evidence-based innovation held elsewhere in medicine (Dondorp and de Wert, 2011; Harper *et al.* 2012, 2017; Sharpe, 2018). This is problematic not just in terms of the good-quality medical care that fertility patients may expect for themselves, but also because possible risks of new assisted reproductive technologies (ARTs) extend to the offspring conceived with these methods. In the light of this, one would expect the field to take the safety of its procedures far more seriously than it currently does. The point was forcefully brought home in a recent review in this journal of the emerging awareness of the relevance of the 'developmental origins hypothesis of health and disease' for responsible innovation in reproductive medicine. As the author observes, 'it seems clear that the techniques applied in ART do actually affect the growth, development and health of offspring, but it is unclear to what extent each of the techniques does so, what the effects are on short and long-term health and what the optimal treatment would be' (Roseboom, 2018).

In the light of these concerns, there is growing support for the view that new reproductive technologies should only be introduced after predictive preclinical efficacy and safety studies (Pennings *et al.*, 2007; Van Steirteghem, 2008; Harper *et al.*, 2012; Provoost *et al.*, 2014; Mulder *et al.*, 2018; Sharpe, 2018). For preclinical research in this field, cellular models, animal models (ranging from rodents to non-human primates) and human embryos can be used, depending on the research question. However, the moral sensitivity of human embryo

research has led to regulations and guidance requiring that the use of human embryos may only be considered for important (basic or preclinical) research questions that cannot be answered through other means, including animal models. We call this the 'use animals first' (UAF) rule.

At the same time, animal research is morally sensitive as well, as is reflected in the growing support of the so-called 3Rs, calling researchers to 'replace, reduce, refine' the use of research animals wherever possible (NC3Rs, 2018). Interestingly, the ethical framework for animal research insists that animals may only be used for research questions that cannot be answered through other means (Jans *et al.*, 2018). As in this context 'other means' would seem to include research using human embryos, researchers may find themselves in a *catch-22* situation regarding the prioritization of these two types of preclinical research. In this paper, we explore the possible moral arguments behind the UAF-rule and test their validity. Although this rule applies to multiple scientific practices, the scope of this paper is limited to preclinical ART research. When referring to human embryos as possible research material, we mean early (<14 days) *in vitro* embryos of sufficient quality that are either donated to research during an IVF-treatment procedure, or embryos especially created for research ('research embryos').

The 'use animals first' rule

As a general rule, the UAF-rule takes the form of a subsidiarity requirement that applies to all forms of human embryo research, regardless of context and purpose. An early example of this can be found in the seminal Warnock report (Warnock, 1985) that has not only stood at the cradle of the British legislation of human embryo research, but has influenced relevant regulations in other countries as well. In this report it is said that 'no one should undertake research on human embryos the purposes of which could be achieved by the use of other animals or in some other way' (p. 63). The argument given for upholding this rule is that 'the human embryo is entitled to some added measure of respect beyond that accorded to other animal subjects' (p. 62). A similar position was taken by the Health Council of the Netherlands in an advisory report commissioned by the Dutch government. According to the report, human embryo research is acceptable only under conditions, including the condition that 'it must not be possible to obtain the envisaged results in any other way (through animal research or cell culture, for example)' (Health Council of the Netherlands, 1998, p. 58). Further examples can be found in professional guidance documents. For example, the International Society for Stem Cell Research (ISSCR) states that human embryo research proposals 'should include a discussion of alternative methods and provide a rationale for […] performing the experiments in a human rather than animal model system' (ISSCR, 2016, p. 6).

In many European jurisdictions, such as the Netherlands, Belgium, the United Kingdom and France, the UAF-rule is enshrined in the law. For example, following the Dutch embryo law, it is permissible to use embryos for research only when there is 'no alternative research method' (CBO, 2003), and in the UK, research on human embryos is only permitted when the Human Fertilisation and Embryology Authority (HFEA) 'is satisfied that any proposed use of embryos […] is necessary for the purposes of the research' (Human Fertilisation and Embryology Act, 1990, p. 60). In order to receive a human embryo research license from the HFEA, 'the scientists applying for a research licence are asked to provide a lot of information about the research they wish to carry out and why the research could not be done using animal embryos or other types of cells' (HFEA, 2017).

Ideal chain of ART research steps

More specifically, in guidance pertaining to preclinical ART research, the UAF-rule translates into a preferred order of research steps in which animal studies precede human embryo research. For instance, according to the Health Council of the Netherlands, the ideal order of research steps involved in the responsible introduction of new ARTs is as follows: 'animal-based experimental research, preclinical research using embryos, randomized trials with patient groups, and follow-up research among the children' (Health Council of the Netherlands, 1998, p. 70). This same order of consecutive steps can be found in the recommendations of ESHRE's Task Force Ethics and Law (Pennings *et al.*, 2007) and more recently in papers of a group of leading ART-scientists, presenting an 'ideal paradigm', or 'pathway' from basic physiological to clinical research through intermediate steps of animal and human embryo research (Brison *et al.*, 2013; Harper *et al.*, 2012, 2017; Mulder *et al.*, 2018). The adjective 'ideal' reflects that in practice this order cannot always be followed. For instance, when a useful animal model is lacking, or when a question cannot be answered in research using human embryos, these steps will have to be skipped. Inevitably that will make it a greater challenge to determine if the step towards first clinical applications can safely be made.

Implications for scientific practice

From a purely scientific point of view, there is no such thing as a preferred order of research-steps other than in terms of always choosing the optimal way of answering a given research question. In preclinical ART research, this may involve the use of different kinds of animal models, but also of human embryos, depending on what would best fit the precise aims of the study. There is not necessarily a conflict between this scientific perspective and the UAF-rule. For example, for many preclinical research questions (e.g. whether a new ART may lead to successful pregnancies in mammals, or to study transgenerational safety effects of new ARTs), human embryos are not suitable to begin with. It is clear that these questions can only be studied in animal models (Mulder *et al.*, 2018; Sharpe, 2018). Where human embryos are suitable (e.g. for studying the possible effect of a new ART on gene expression patterns during embryonic development), doing the same research with animal embryos would not be as informative, given the translational distance between those species and humans. As in such a case the same question cannot be answered in research using animal embryos, the UAF-rule does not stand in the way of directly moving to human embryo research.

The notion of an 'ideal chain' reflects however a more extensive interpretation than the above strict reading of the general rule. According to this interpretation, human embryo research should only be considered after promising results have first been obtained in animals, or when it is clear that animal studies cannot contribute at all to answering the question. When following this interpretation, research ethics committees will not allow scientists to directly move to human embryo research as long as prior animal studies might still lead to

results that are at least partially relevant to answering the research question. Again, this is not necessarily at odds with the more pragmatic perspective of science, which always requires balancing the pros and cons of different approaches, including issues such as costs, uniformity and easy availability in large numbers. However, deciding this on a case by case basis is not possible when research ethics committees take the line that animal research should always precede the use of human embryos regardless of how useful that prior step would be. Our impression is that researchers in the field of ART often face difficulties receiving permission for human embryo research when data from prior animal studies, more specifically: studies using animal embryos, are lacking. This is ethically problematic in so far as it may lead to a waste of valuable research time and money, but also because it violates a core principle of the ethics of animal research, namely that the inevitable impact on animal wellbeing should be proportional to the importance of the benefits to be gained through that research (Jans *et al.*, 2018).

The morality of interests

Apart from the quoted line in the Warnock report, we did not come across any specific ethical justifications for the UAF-rule. It seems to be taken for granted that using human embryos as research material is morally more problematic than using animals and should therefore only be considered when (further) studies using an animal model will not contribute to the answer of the research question. But how strong is the argument for this position? In this section, we consider what animals stand to lose when being used as research material and ask how the fate of human embryos compares to this.

The strong consensus acknowledges that, in contrast to mere tissues and cells, animals have a moral standing, which means that we are obliged to consider their needs and interests when making decisions affecting them (Warren, 1997). Philosopher McMahan describes this as the 'morality of interests' (MoI), which refers to how the interests of beings at the receiving end of our actions constrain what we may do to them (McMahan, 2002). This view is reflected in the European animal research legislation, which incorporates the Three Rs; Replace, Reduce and Refine the use of animals for research (European Union, 2010).

The more the use of animals in research leads to pain, discomfort, a negative psychological impact, or an infringement of species-specific behavior, the greater the human benefits must be in order for the research in question to be considered proportional. Preclinical animal research for testing new ARTs has a relatively low impact on the wellbeing of animals, as compared to animal research in other contexts, such as certain forms of cancer or burns research (Jans *et al.*, 2018). Nevertheless, all animals in research suffer some extent of discomfort and/or pain. As preimplantation human embryos by contrast are not capable of experiencing pain or psychological distress, embryo research does not have an impact on their wellbeing. Choosing human embryos instead of animals (when both can be used for answering the research question) would reduce the total negative impact on wellbeing and would in so far be morally preferable.

A reduced level of wellbeing is not the only way in which interests can be harmed; also premature death can do so and – at least in humans – taking a life is generally considered to be the greatest possible infringement on the victim's interests. In ART research, all animals (except non-human primates) will ultimately be painlessly killed. Following McMahan, the wrongness of killing depends on (1) the amount of good a being loses by dying and (2) the strength of its time-relative interest in continuing to live. This strength is dependent on whether, and if so how strongly, a being is psychologically connected to its future self (McMahan, 2002). In this context, it is less wrong to kill lower animals (e.g. mice) than higher animals (e.g. non-human primates), as the latter would lose a more psychologically complex life and are more strongly connected to their future life because of their higher psychological features.

What about killing human embryos in or after research? Does this deprive them of a future life? Clearly, if left-over IVF-embryos are used, this is not a meaningful question, as those embryos are destined to perish already prior to being considered as research material (Pennings and Van Steirteghem, 2004). However, what if human embryos are especially created to serve as research material? Could one argue that they are *ab initio* deprived of a more valuable future life than even the highest animal? This 'future like ours argument' has been applied to the ethics of abortion by philosopher Don Marquis (Marquis, 1989). But whatever its worth in that context, the argument cannot simply be extended to make the case that preimplantation embryos would be deprived of 'a future like ours'. Such deprivation would require a level of connection of a present self to a future self that goes beyond what can be attributed to an embryo. We conclude that the MoI does not support the UAF-rule. In fact, it would seem to rather support the opposite.

The morality of respect

A second possible line of argument is that a special moral status can be attributed to human embryos regardless of whether they can be said to have interests. A reference to this special moral status can, for example, be found in the quoted argument from the Warnock report (Warnock, 1985).

An argument to support this claim would have to explain what morally distinguishes human embryos from animals. This cannot be the simple fact that they are 'human', as that would amount to a speciesist fallacy. If the argument can be made, it must somehow connect with *why* we think human beings have a special moral status and then, secondly, explain what this entails for human embryos. The main non-religious answer to the first part of this question is that we consider (most) humans to be 'persons' (DeGrazia, 1997; Warren, 1997; Harris, 1999), which means that they have a high 'enough' degree of personhood properties, such as 'moral agency, autonomy, the capacity for intentional action, rationality, self-awareness, sociability and linguistic ability' (DeGrazia, 1997, 2008, p. 193).

McMahan speaks of what we owe to persons in terms of the 'Morality of Respect' (MoR). Even if some animals (great apes) may perhaps qualify as borderline persons (DeGrazia, 1997), animals generally fall below what he calls the 'person threshold', which means that they are not entitled to the same degree of protection as human individuals. Whereas the use of persons as 'mere means' is morally unacceptable, this does not hold for beings below this threshold: using them for entirely instrumental purposes can be acceptable under conditions (Jans *et al.*, 2018).

What does this mean for a possible special moral status of early human embryos? Only for those who regard these as persons does their moral status have the weight accorded by the MoR. Most people,

however, accord a more limited moral status to the human embryo. This is often argued for in terms of those embryos having the capacity to develop into human beings who will then be persons. Clearly, this is not enough to grant them the full protection of the MoR, given that even as 'potential persons', they are not persons yet. In fact, the widely endorsed understanding is that in comparison with that of persons, the special moral status of human embryos and fetuses is initially quite low and only increases with *in utero* development. Still, this is in comparison with persons, not with animals, to whom such a special moral status is not ascribed at all (apart perhaps from great apes as borderline persons (DeGrazia, 1997)). The reference to 'an added measure of respect' in the Warnock report suggests that it is on this difference between human embryos and animals that the UAF-rule rests. However, it is silent about the opposite conclusion that seems to follow from the MoI.

The interests of oocytes donors

For preclinical safety and efficacy studies in the context of introducing new ARTs, it will often not be possible to do the research with spare embryos that are left over from IVF treatment. In those cases, research embryos will need to be especially created for the purpose, which requires the use of donated human oocytes. As oocyte donation for the benefit of science is a morally sensitive practice, this might be regarded as an argument for the UAF-rule, at least in cases where the use of spare embryos is not an option. In order to produce mature oocytes, the donor must undergo hormone stimulation and oocyte pick-up. The procedure is burdensome and may entail physical risks, including a risk of the woman developing ovarian hyper stimulation syndrome (OHSS). However, with careful protocols these risks can almost completely be avoided (Devroey *et al.*, 2011). Still, in the light of the demanding nature of the procedure, not many women are willing to volunteer. Indeed, some commentators have argued that the creation of embryos for the purpose of research can increase the risk of coercion for women (Baylis, 2000) or might threaten women's autonomy (Gerrand, 1993). Financial compensation schemes or so-called egg-sharing procedures (in which IVF-patients are offered free or reduced-cost treatment in return for donating part of the mature oocytes obtained in the process (Blyth, 2002)) have been criticized for inviting exploitation of vulnerable women. Here again, however, these risks can be minimized with carefully designed practices of information, counseling and consent (Mertes and Pennings, 2006). Although it is certainly true that the challenges of responsibly obtaining mature human oocytes for preclinical embryo research are an argument for using spare embryos whenever the research question can be answered with these as well, we think it is difficult to maintain that these challenges are so large as to settle the issue in favor of the UAF-rule. Moreover, it is expected that with new sources of research oocytes, including oocytes left over from cryostorage for fertility preservation (Mertes *et al.*, 2012), immature oocytes grown and matured *in vitro* (McLaughlin *et al.*, 2018), and stem cell derived oocytes (Segers *et al.*, 2017), any remaining moral challenges will eventually be overcome.

Conclusion and recommendations

Apparently, the UAF-rule is based on the view that human embryos have a special moral status, without including the MoI perspective. When both perspectives are included, it is less clear that the UAF-rule is morally tenable. In light of this, different scenarios can be considered. When doing so, we leave aside any possible legal barriers to using or creating human embryos for research that exist in certain countries. Assuming that these research options are not categorically forbidden and therefore unavailable, let us first consider the scenario of preclinical research for which left-over IVF-embryos could be used. As said, those embryos are destined to perish already prior to being considered as research material. Using them for research only determines how they will perish, not whether they will. To maintain that it would still be morally preferable not to make use of those embryos, but to create and use animals instead (even if only as sources of gametes and embryos), strikes us as perverse. However, preclinical ART research cannot always be performed with left-over IVF embryos. As said, it will often be necessary to create embryos for the purpose. Would that change matter? If human embryos have a special moral status, they should not be created for research that can also be carried out with morally less offensive research material. But again: is that the case where animals are concerned that would also have to be created for the purpose? The least one should say, is that this is not obvious, not even with the possible support from the argument pertaining to the morality of asking women to act as oocyte donors. We conclude that the moral arguments to support the UAF-rule are not evidently weightier than arguments supporting the opposite view, according to which animals deserve more protection than human embryos.

As no overriding moral arguments supporting the UAF-rule were found, we wonder why this rule is so widely supported. Our hypothesis is that it is based on 'human prejudice', which in this case invites the view that human embryos deserve more respect than even the highest animal, solely because they belong to the 'human species' (Savulescu and Bostrom, 2009). Obviously, this is no valid argument to uphold the UAF-rule.

We recommend that in legal documents and professional guidance, the UAF-rule is abandoned and replaced by a justificatory framework that does not *a priori* favor animal studies over the use of human embryos in research. The notion of a chain of ART research steps should be modified accordingly. A core message must remain that the step to the clinic can only responsibly be made after adequate preclinical safety studies. Clearly, this should include animal studies aimed at charting potential health effects of new reproductive technologies at multiple stages of offspring development in more than one generation (Mulder *et al.*, 2018; Sharpe, 2018). However, it should also include early developmental (e.g. gene expression) research done directly on human embryos that would bypass the uncertainties that go with animal-based studies (Brison *et al.*, 2013). With potentially risky reproductive technologies on the horizon (such as reproduction using stem-cell derived gametes, or genetically modified gametes or embryos), it is important that optimal use can be made of either type of morally sensitive research material. As the ill-founded notion of the greater moral sensitivity of human embryo research may stand in the way of this, it should be abandoned so as to avoid waste and increase the relevance of preclinical safety research. In line with this, research ethics committees assessing protocols for the use of human embryos in preclinical ART research should refrain from requiring prior animal studies that are not expected to be informative.

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All authors contributed to the conception and design of this paper. The first author has drafted the article, but all authors contributed in

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Conflict of interest

The authors declare that they have no conflict of interest.

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